

## LA-UR-19-29355

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Author(s): Larkin, Ariana Kayla

Intended for: Report

Issued: 2019-09-17

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# An Innovative HIV “Mosaic” Vaccine Design Based on Machine Learning

Janssen Pharmaceutical Companies of Johnson & Johnson, The Bill and Melinda & Melinda Gates Foundation, National Institutes of Health, Harvard and Duke.

*Los Alamos research was fundamental to an efficacy trial for evaluating a mosaic HIV-1 preventive vaccine*

## Innovation

Approximately 37 million people worldwide have the human immunodeficiency virus (HIV). Because of HIV’s incredible diversity — each infected person carries a unique set of viruses — an effective vaccine against HIV needs to stimulate an immune response that can recognize its many variants.

Using a machine-learning algorithm and the NIH funded Los Alamos National Laboratory database of hundreds of thousands of HIV sequences gathered from around the globe, Los Alamos scientists were able to design small sets of sequences that in combination provide optimal coverage of HIV’s diversity.<sup>1</sup>

The mosaic vaccine is the world’s first computationally-designed vaccine. Through a decade of testing it has continued to show promise, and so currently is being tested in two human efficacy trials to evaluate whether the investigational vaccine regimen can reduce the incidence of HIV infection among 2,600 women in sub-Saharan Africa, and 3,800 men who have sex with men and transgender people in the Americas.<sup>2</sup>

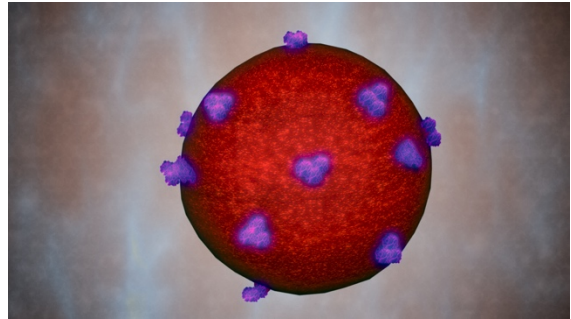
## Technology Advancement

Los Alamos funded the initial work on the theoretical aspects of the mosaic design concept. The National Institutes of Health then funded the HIV mosaic experimental development through collaborations with Duke and Harvard.

Mosaic vaccines are designed using thousands of protein sequences extracted from the Los Alamos database, an NIH funded project to track HIV’s global diversity.<sup>3</sup> The mosaic algorithm was inspired by the way HIV itself evolves. The problem that it solved is how to design a small set of complementary sequences that resemble natural proteins and in combination best capture the global diversity of the virus.

## Impact

The mosaic vaccine concept is applicable not only to HIV but to other variable pathogens as well, thus having a potential for far ranging impact on public health and national security. We have also designed HIV conserved region mosaics for testing as a possible therapeutic vaccine.<sup>4</sup> Mosaic designs are in various stages testing for other viruses, including a foot-and-mouth disease and Hepatitis B and C.<sup>5</sup> LANL scientists also designed a filovirus vaccine against Ebola and Marburg viruses, using a graph-based variant of the mosaic approach.<sup>6,7</sup>



Machine learning HIV virus.

“We selected Bette as our 2018 Scientist of the Year to recognize not only her groundbreaking contribution to the mosaic vaccine and the fight against HIV, but also for her continued commitment to trying new and innovative scientific approaches,”

- Bea Riemschneider, Editorial Director, R&D Magazine

## Timeline

**2005:** The theory/computational work for the HIV mosaic vaccine design was initiated at Los Alamos.

**2007:** The original mosaic design and theory was first published in 2007.<sup>1</sup>

**2010:** Mosaic vaccines were shown to be immunogenic and elicit more potent immune response than natural proteins<sup>8</sup>

**2013:** Mosaic vaccines were shown to dramatically reduce the rate of viral infections in monkeys.<sup>9</sup>

**2018:** Mosaic vaccines were shown to be safe and to elicit strong immune responses in humans.<sup>10</sup>

**2018:** Bette Korber: R&D Magazine Scientist of the Year and Feynman Innovation Prize winner for the Mosaic design concept.

**2018 & 2019:** Clinical efficacy trials initiated in Africa (Imbokodo, results expected 2021) and the Americas (Mosaico, results expected in 2023).<sup>2</sup>

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<sup>1</sup> *Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants.* Fischer W, Perkins S, Theiler J, Bhattacharya T, Yusim K, Funkhouser R, Kuiken C, Haynes B, Letvin NL, Walker BD, Hahn BH, Korber BT. *Nat Med.* 2007 Jan;13(1):100-6. **First mosaic vaccine theory paper: LANL funded mosaic theory and design, PI: Korber.**

<sup>2</sup> NIH News Release, July 15, 2019: NIH and partners to launch HIV vaccine efficacy trial in the Americas and Europe

<sup>3</sup> The NIH Los Alamos HIV Database project was founded by Dr. Gerald Myers at Los Alamos National Laboratory in the late 1980s, and was the first pathogen database. It is still an ongoing database resource used by HIV researchers worldwide; typically the HIV database website has over 500,000 hits and ~30,000 interactive uses per month, and it currently holds over 900,000 curated HIV-1 sequences. ([www.hiv.lanl.gov](http://www.hiv.lanl.gov)). Bette Korber has been the PI of the project since 1994. **NIH funded HIV database project, PI: Korber.**

<sup>4</sup> *Novel Conserved-region T-cell Mosaic Vaccine With High Global HIV-1 Coverage Is Recognized by Protective Responses in Untreated Infection.* Ondondo B, Murakoshi H, Clutton G, Abdul-Jawad S, Wee EG, Gatanaga H, Oka S, McMichael AJ, Takiguchi M, Korber B, Hanke T. *Mol Ther.* 2016 Apr;24(4):832-42. **HIV conserved region vaccine, possible applications for prevention or therapy. Design and analysis, NIH funded: Duke PI: Barton Haynes, LANL local PI: Bette Korber. Testing: NIH funded: Duke PI: Barton Haynes; and UK Medical Research Council and others... Oxford PI: Tomas Hanke.**

<sup>5</sup> *Hepatitis C genotype 1 mosaic vaccines are immunogenic in mice and induce stronger T-cell responses than natural strains.* Yusim K, Dilan R, Borducchi E, Stanley K, Giorgi E, Fischer W, Theiler J, Marcotrigiano J, Korber B, Barouch DH. *Clin Vaccine Immunol.* 2013 Feb;20(2):302-5. **LANL funded design, PI: Korber, NIH funded testing, Harvard PI: Dan Barouch.**

<sup>6</sup> *Graph-based optimization of epitope coverage for vaccine antigen design.* Theiler J, Korber B. *Stat Med.* 2018 Jan 30;37(2):181-194. And *Epigraph: A Vaccine Design Tool Applied to an HIV Therapeutic Vaccine and a Pan-Filovirus Vaccine.* Theiler J, Yoon H, Yusim K, Picker LJ, Fruh K, Korber B. **Ebola vaccine design using Epigraph, using a graph-based variant of the mosaic approach also developed at Los Alamos National Lab. LANL initiated funding for Epigraph theory and Filovirus vaccine design and initial experiments, followed by Gates foundation funding: LANL PI and GATES local LANL PI: Korber and GATES PI: Louis Picker, University of Oregon.**

<sup>7</sup> *Complete protection of the BALB/c and C57BL/6J mice against Ebola and Marburg virus lethal challenges by pan-filovirus T-cell epigraph vaccine.* Rahim MN, Wee EG, He S, Audet J, Tierney K, Moyo N, Hannoun Z, Crook A, Baines A, Korber B, Qiu X, Hanke T. *PLoS Pathog.* 2019 Feb 28;15(2):e1007564. **Testing the Ebola/Marburg vaccine in an animal model. Several funding groups contributed to this.**

<sup>8</sup> *Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys.* Barouch DH, O'Brien KL, Simmons NL, King SL, Abbink P, Maxfield LF, Sun YH, La Porte A, Riggs AM, Lynch DM, Clark SL, Backus K, Perry JR, Seaman MS, Carville A, Mansfield KG, Szinger JJ, Fischer W, Muldoon M, Korber B. *Nat Med.* 2010 Mar;16(3):319-23. And: *Mosaic vaccines elicit CD8+ T lymphocyte responses that confer enhanced immune coverage of diverse HIV strains in monkeys.* Santra S, Liao HX, Zhang R, Muldoon M, Watson S, Fischer W, Theiler J, Szinger J, Balachandran H, Buzby A, Quinn D, Parks RJ, Tsao CY, Carville A, Mansfield KG, Pavlakis GN, Felber BK, Haynes BF, Korber BT, Letvin NL. *Nat Med.* 2010 Mar;16(3):324-8. **Testing mosaic vaccine responses in a rhesus macaque model. NIH funding, Harvard PI: Dan Barouch, Duke PI: Barton Haynes, LANL local PI: Bette Korber**

<sup>9</sup> *Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys.* Barouch DH, Stephenson KE, Borducchi EN, Smith K, Stanley K, McNally AG, Liu J, Abbink P, Maxfield LF, Seaman MS, Dugast AS, Alter G, Ferguson M, Li W, Earl PL, Moss B, Giorgi EE, Szinger JJ, Eller LA, Billings EA, Rao M, Tovanabutra S, Sanders-Buell E, Weijtens M, Pau MG, Schuitemaker H, Robb ML, Kim JH, Korber BT, Michael NL. *Cell.* 2013 Oct 24;155(3):531-9. **Mosaic vaccines can confer protection from infection in and HIV animal model. NIH funding, Harvard PI: Dan Barouch.**

<sup>10</sup> *Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19).* Barouch DH, Tomaka FL, Wegmann F, Stieh DJ, Alter G, Robb ML, Michael NL, Peter L, Nkolola JP, Borducchi EN, Chandrashekar A, Jetton D, Stephenson KE, Li W, Korber B, Tomaras GD, Montefiori DC, Gray G, Frahm N, McElrath MJ, Baden L, Johnson J, Hutter J, Swann E, Karita E, Kibuuka H, Mpendo J, Garrett N, Mngadi K, Chinyenze K, Priddy F, Lazarus E, Laher F, Nitayapan S, Pitisuttithum P, Bart S, Campbell T, Feldman R, Lucksinger G, Borremans C, Callewaert K, Roten R, Sadoff J, Scheppler L, Weijtens M, Feddes-de Boer K, van Manen D, Vreugdenhil J, Zahn R, Lavreys L, Nijs S, Tolboom J, Hendriks J, Euler Z, Pau MG, Schuitemaker H. *Lancet.* 2018 Jul 21;392(10143):232-243. **Mosaic vaccine is safe and immunogenic in people. Project lead by Dan Barouch at Harvard, and Hanneke Schuitemaker at Janssen. Bette Korber just helped a little with analysis. Many agencies funded this, as well as J&J and Janssen.**